

**REMARKS**

**I. Claims**

By this paper, claims 1, 10, 11, 13, 20, 22 and 23, have been amended to state that the sweetening agent comprises a mixture of aspartame and potassium acesulfame. The basis for this amendment can be found in the specification at page 7, lines 10-15 and in the original Claims 4 and 5, now cancelled. Further, the indefinite terms "effective amount(s)" have been removed from Claims 1, 6, 10, 11, 13, 20, and 23 without altering the scope of the claims.

A new claim 33 has been added. Claim 33 finds support in original Claim 1 with the limitations of original Claim 4. Claims 4-5, 16-17, and 27-28 have been cancelled.

Upon entry of this Amendment B, claims 1-3, 6-15, 18-26 and 29-33 will be pending in the application.

**II. Claims Rejection 35 USC § 112**

1. Reconsideration is requested of the rejection of claims 1, and 4-6 under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner has asserted that one of ordinary skill in the art could not ascertain the metes and bounds of the term "aromatic flavoring agent". Applicant respectfully submits that the term "aromatic flavoring agent" is a term of art easily appreciated by one skilled in the art. The office has allowed the use of this term and its variants in claims; see for example US Patent Nos. 4,925,637; 5,017,385; 5,077,068; 6,544,551; 6,916,463; etc. Flavoring agents are ubiquitous in the food and beverage industry for imparting desirable taste, and in the pharmaceutical industry for masking bitter and undesirable tastes, and are available commercially. The term is well known in the art; hence, applicant respectfully submits that the term "aromatic flavoring agent" in the claims including claim 1 is not vague and indefinite. Applicant respectfully requests withdrawal of this rejection.

Claims 4 and 5 have been cancelled hence their rejection is moot.

2. Reconsideration is requested of the rejection of claims 10, 13-17, and 20-22 under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner has asserted that the term "effective amounts being selected so as to mask substantially the bitter taste and pungent odor of sodium 4-phenylbutyrate" and similar phrases are indefinite. Applicant respectfully submits that the amount used will depend on the amount of sodium 4-phenylbutyrate present and as such one cannot give an absolute value or even a range. However, the skilled man would readily be able to tell whether he has achieved the necessary level because the question will be whether the composition is palatable. It should also be borne in mind that this is a product that is generally destined for children and therefore their tolerance to taste and smell is much less than the tolerance of an adult; adults will put up with unfortunate taste because they know the product composition is doing them good. Thus the skilled man simply has to carry out a very routine test as to whether a child will take the product and then he will know whether he has masked the taste.

However, in order to facilitate prosecution, the indefinite term "effective amount(s)" has been deleted from the claims. This deletion does not alter the scope of the claims in any way.

Claims 16 and 17 have been cancelled thus rendering their rejection moot.

3. Reconsideration is requested of the rejection of claims 13-17, and 20-21 under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner rejected Claims 13 to 17 and 20 to 21. Claims 13 and 20 have been amended to insert "to" into the expression "up to the solubility limit thereof measured at 10 degrees C" so as to correct a typographical error.

Claims 14-17 and 21 are dependent claims depending from claims 13 and 20 respectively, and are patentable for the same reasons as Claims 13 and 20.

4. Reconsideration is requested of the rejection of claims 23-28 under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner has asserted that use of the language "a binding amount of binding agent" in Claim 23 is vague and indefinite and that the specification does not provide information as to how much is the binding amount of a binding agent that can be used. This amount will of course vary with the respective amounts of the other components used. The skilled man would readily be able to work out the amount of a specific binding agent required to bind a particular composition.

Claims 24-28 are dependent claims depending from claim 23, and are patentable for the same reasons as claim 23.

5. Reconsideration is requested of the further rejection of claims 23-28 under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The indefinite term "sufficient" in line 9 of Claim 23 has been deleted without affecting the scope of the claim; the goal here is to mask substantially the bitter taste of the drug, sodium 4-phenylbutyrate.

Claims 24-28 are dependent claims depending from claim 23, and are patentable for the same reasons as claim 23.

6. Reconsideration is requested of the further rejection of claims 23 and 31 under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 has been amended to overcome the indefiniteness regarding the limitation "artificial water soluble sweetening agent". Claim 31 has been amended to correct the typographical error, i.e., "softening sweetening".

### **III. Rejection of Claims 1-6, 9 and 10 under 35 USC § 103**

Reconsideration is requested of the rejection of claims 1-6, 9 and 10 under 35 USC § 103(a) as being unpatentable over Samid et al. (US 6,037,376, PTO-892) in view of Rubenstein et al. (US 2002/0115619, PTO-892), and further in view of Blasé et al. (US 5,272,137, PTO-892).

The Examiner has suggested that claims 1-6, 9 and 10 lack inventive step over the combined teachings of Samid, Rubenstein and Blasé.

As a background to the present invention, to date, children have been refusing the needed treatment because phenylbutyrate is very bitter and the dose required for the treatment regime is very high. In this connection, applicant would like to draw the Examiner's attention to an article; Dover et al., Blood 84, 339-343 1994 (of record in IDS), which states "a major drawback to the use of phenylbutyrate is the high dose. The usual adult dose (20g daily) requires taking 40x 0.5g tablets. Although the number of tablets will be less in children, this REPRESENTS A SIGNIFICANT PROBLEM IN USE AND PATIENT COMPLIANCE with a therapeutic regime. The drug in powder form has a BITTER TASTE that, DESPITE MANY ATTEMPTS, CANNOT BE DISGUISED. Two of the three subjects treated after discharge from the hospital reported INABILITY TO MAINTAIN COMPLIANCE. However, if clinical efficacy can be shown, THE INGENUITY of pharmaceutical manufacturers MIGHT SURMOUNT this problem" (Emphasis added).

In other words, most of the children rejected treatment with phenylbutyrate because of the taste and could not be treated. The clinical trial was for the use of sodium phenylbutyrate to treat sickle cell anaemia. This is an, as yet, unproven treatment. However, phenylbutyrate is efficacious for the treatment of urea cycle disorders. The licensed products are either 500mg tablets or granules of 940mg/g. The granules are very bitter and are dispensed using three calibrated scoops. This is not an accurate way of administering the dose. It would be much better to measure a solution containing 250mg phenylbutyrate in 1ml using an oral syringe calibrated in 0.01ml increments.

Phenylbutyrate is too bitter to be made palatable with sucrose. In any case, modern medicines have to be sugar free and colorant free. The Acceptable Daily Intake (ADI) of the

sweeteners available to produce an oral product acceptable to children are set out in Table 1 of the specification.

Aspartame is the sweetener with the most acceptable taste. However, its use is limited in liquids because of its low solubility and fairly rapid hydrolysis in water to form phenylalanine which itself is bitter. Unfortunately, aspartame is not ideally suited for use in dispersible tablets for children due to its slow rate of dissolution; it takes approximately 3 minutes to form a 1% w/v solution.

Therefore to prevent hydrolysis, aspartame is mixed with phenylbutyrate powder and a flavor and put into a 100 ml medicine bottle. The powder is made into a liquid immediately before use and a pharmacist adds 80ml purified water to the 100ml bottle.

The solubility of the sodium phenylbutyrate in water is about 265mg in 1ml. To facilitate ease of calculation of doses, sufficient (i.e. 25g) phenylbutyrate is added to the bottle to make 100ml of a 250mg per ml solution.

The amount of aspartame to be added depends on its solubility and the amount required to sweeten the maximum dose of phenylbutyrate (600mg per kg per day).

The maximum dose of sodium phenylbutyrate for children is 600mg/kg body weight per day. In spite of this being very high, the ADI of each sweetener must not be exceeded.

The solubility of aspartame is only 1% w/v (10mg in 1ml) which limits the amount which can be given in a concentrated solution as sodium phenylbutyrate. Therefore, the 250mg of sodium phenylbutyrate in 1ml can only be sweetened with 10mg of aspartame. The intake of a maximum of 600mg per kg dose of sodium phenylbutyrate is 24mg per kg ( $10 \times 600 / 250$ ). This is well below the ADI (40mg/kg) but is insufficient to sweeten the phenylbutyrate acceptably. Therefore, another powerful sweetener is required.

Sodium saccharin is undesirable since the high dose of sodium phenylbutyrate represents a high sodium intake. To minimize sodium intake, potassium acesulfame is selected as the secondary sweetener.

The ADI for potassium acesulfame is 15mg/kg/day. In the preferred embodiment it was decided by the inventors to use just slightly less so that the 250 sodium phenylbutyrate was sweetened with 6mg acesulfame potassium. It was surprisingly found that this was sufficient

to make the product palatable if the concentrated solution was diluted with 9 parts water to form a 25mg long drink that was sipped.

Table 2 sets out the intake of artificial sweeteners at the maximum dose of 600mg/kg/day sodium 4-phenylbutyrate.

In addition, the present invention being a composition which includes a mixture of aspartame and potassium acesulfame has the added advantage of not requiring microbiological preservatives since sodium phenylbutyrate in the solution prevents bacterial growth.

It will therefore be understood that:

1. Sodium phenylbutyrate dissolves very slowly so it is not practical to formulate a 250mg sodium 4-phenylbutyrate tablet that dissolves in an acceptable time frame, i.e., less than 1 minute. That necessitates the formulation of liquid.
2. Aspartame is hydrolyzed in water to form a bitter solution of phenylalanine. Therefore, any solution, made with aspartame has to be prepared no more than a month before consumption. That necessitates a dry powder to be made up with water just before use.
3. Although aspartame is the sweetener with the most acceptable taste, it has been discovered that a secondary sweetener was also required.
4. The combination of aspartame and potassium acesulfame was found to offer significant advantages.

The Examiner has suggested that since in his opinion Samid discloses pharmaceutical compositions comprising sodium phenylbutyrate, a water soluble sweetening agent and sugar, and Rubenstein features that it has a bad taste and that a sweetener should be used, and Blase teaches that sweeteners are used in the pharmaceutical industry to mask bad tastes, it would be obvious to combine the teachings of all three arts to arrive at the present application. This is simply incorrect in view of the particular problems associated with sodium 4-phenylbutyrate. Indeed the enclosed journal article makes it clear that the general understanding of the industry was that the problems associated with phenylbutyrate were so

great that they were unlikely to be solved without THE INGENUITY of the pharmaceutical manufacturers. It is this ingenuity that the applicants have now shown. Applicant therefore submits that the claims of the current application are patentable over Samid et al. in view of Rubenstein et al. and further in view of Blasé et al.

**CONCLUSION**

In view of the foregoing, applicant respectfully requests removal of the rejections and allowance of the claims.

Applicant requests an extension of the period for responding to the Office Action by 2 months by inclusion of the appropriate fee. The Commissioner is hereby authorized to credit any overpayment or charge any underpayment of Government fees to Deposit Account No. 19-1345.

Respectfully submitted,

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